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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/799,782	03/15/2004	Axel Ullrich	017853-0145	9104

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EXAMINER	
SPECTOR, LORRAINE	
ART UNIT	PAPER NUMBER
1647	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/799,782	ULLRICH ET AL.	
	Examiner	Art Unit	
	Lorraine Spector	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5 and 6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5 and 6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Interpretation

It is noted that the recitation in claims 5 and 6 of "cell line" is taken to indicate an *in vitro* cell population, and not to read on an animal or human.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 5-6 remain rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent No. 5,851,999. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1-4 would be anticipated by the patented claims, as the claims are related as sub-genus to genus. With respect to claims 5 and 6, the person of ordinary skill in the art would immediately grasp, upon reading the patented claims, the desirability of making a cell line as currently claimed to produce the viral particles used in the patented pharmaceutical compositions. Accordingly, the claims are obvious over the patented claims.

In the response filed 3/18/2009, applicant argues that the proposed modification would change the principal of operation of the pharmaceutical composition. This argument has been fully considered but is not deemed persuasive because the recitation "pharmaceutical composition", which appears in the preamble, merely indicates intended use. It remains that to *make* the claimed composition, one would have to produce the viral particles in a cell line, as claimed herein. Applicants have not addressed this point. Applicant also argues that a cell line is not an obvious variant or modification of a pharmaceutical composition. This argument has been fully considered but is not deemed persuasive because (a) as applicants argument pertains to administration of a foreign cell line, it is, as above, drawn to the intended use, and not to the claimed cell line. (B) Even *if, in arguendo*, the intended use were given weight, there is no prohibition from using the patient's cells to form the cell line.

Accordingly, the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 5-6 remain rejected under 35 U.S.C. § 103 as being unpatentable over Lemischka, U.S. Patent Number 5,185,438, Matthews et al. (PNAS 88:9026) and Terman et al. (BBRC 187:1579), in view of Ullrich et al. (Cell 61:203), and Ueno et al., (Science 252:844, Ueno-1 and JBC 267:1470, Ueno-2), all references cited by applicants.

In the response filed 3/18/2009, applicants argue that none of the cited references disclose that Flk-1 functions as a dimmer, and therefore, activity of a Flk-1 mutant can not be predicted based on the activity of kinase receptor dimer mutants. This argument has been fully considered but is not deemed persuasive because with respect to Terman, Terman teaches that it would be desirable to investigate the dimeric combinations in which the receptor occurs; Terman does not doubt that the receptor *is* a dimer. With respect to Ullrich, combination of the subunit of SEQ ID NO: 2 *in vivo* in a cell that expresses Flk-1 would inherently result in combination with a "normal" subunit, regardless of whether the receptor were a homo- or hetero-dimer.

Applicants remaining arguments bridging pages 6-7 argue the references separately, rather than in the combination in which they are cited, and therefore are non-persuasive.

At page 7, applicants argue that it is not *known* whether KDR and *flt* can form functionally active dimers analogous to the PDGF receptor dimers, or mediate mitogenic activity and/or vascular permeability. This argument has been fully considered but is not deemed persuasive. With respect to the first point, applicants are reminded that Ullrich et al. (Cell 61:203) disclose that "Receptor oligomerization is a universal phenomenon among growth factor receptors" (page 203, second column). At page 206, Ullrich et al. discuss various experiments in which alterations were made to the protein kinase domain of receptors, including the deletion thereof. They state that "While the kinase activity of the various receptors was dispensable for their expression and targeting to the cell surface, it was indispensable for signal transduction and induction of both early and delayed cellular responses, including mitogenesis

and transformation. Therefore, without knowing the subunit structure of the receptor, one would expect that a subunit lacking the tyrosine kinase domain would have dominant negative signaling effects. With respect to the both points, applicants are arguing limitations that are not found in the claims. The claims require neither a dimer, nor any particular activity.

At page 7, applicants argue that "Because *flt1* was a known VEGF receptor with high affinity for VEGF, it was unexpected that the *flk-1* mutant would inhibit the cellular effects of VEGF binding." This argument has been fully considered but is not deemed persuasive because Matthews et al. disclose a recombinant vector comprising cDNA which encodes Flk-1 (See Figure 1). In the abstract, Matthews et al. disclose that *Flk-1* has strong homology to the c-Kit subfamily of receptor kinases, and in particular to the *Flt* gene product. Accordingly, the most parsimonious explanation is that they are homologues and would bind the same ligand (VEGF). Applicants invention follows the teachings of the prior art, and achieves exactly the result that would be predicted on the basis of the prior art. There are no unexpected results.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector. Dr. Spector can normally be reached Monday through Friday, 8:00 A.M. to 2:00 P.M. at telephone number 571-272-0893.

If attempts to reach the Examiner by telephone are unsuccessful, please contact the Examiner's supervisor, Dr. Manjunath Rao, at telephone number 571-272-0939.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to **571-273-8300**. Faxed draft or informal communications with the examiner should be directed to ***571-273-0893.***

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Lorraine Spector/ , Ph.D.
Primary Examiner
Art Unit 1647